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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,811	04/29/2005	Jesus G Valenzuela	4239-67028-08	7353

36218 7590 01/25/2008  
KLARQUIST SPARKMAN, LLP  
121 S.W. SALMON STREET  
SUITE #1600  
PORTLAND, OR 97204-2988

EXAMINER	
BASKAR, PADMAVATHI	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
01/25/2008	PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/533,811	<b>Applicant(s)</b> VALENZUELA ET AL.	
	<b>Examiner</b> Padmavathi v. Baskar	<b>Art Unit</b> 1645	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 04 September 2007.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1,2,4-8,10-21,23-26,28-31 and 34-38 is/are pending in the application.
- 4a) Of the above claim(s) 7,8,10-21,24-26,28-31 and 34-38 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,2,5,6 and 23 is/are rejected.
- 7) ☒ Claim(s) 4 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>7/1/05 and 7/3/06</u> .                                       | 6) <input type="checkbox"/> Other: _____                          |

## DETAILED ACTION

### *Response*

1. Applicant's response to restriction requirement filed on 9/4/07 is acknowledged.

### *Election/Restriction*

2. Applicants elected Group I (claims 1-6 and 23, in part), drawn to a substantially purified salivary *Lu. longipalpis* polypeptide and a composition comprising said polypeptide, SEQ ID NO: 15 (referred to as LJL143 in the specification) for prosecution.

It is regretted the oversight made in the previous Office action in not acknowledging the preliminary amendment submitted on April 29, 2005. The preliminary amendment, April 29, 2005 is entered. Accordingly claims 3, 9, 22, 27, 32, and 33 have been canceled.

### *Status of claims*

3. Claims 1, 2, 4-8, 10-21, 23-26, 28-31, and 34-38 are pending in this application.  
Claims 3, 9, 22, 27, 32, and 33 have been cancelled.  
Claims 1-2, 4-6 and 23 with respect to SEQ ID NO: 15 (referred to as LJL143) are under examination.

Claims 7-8, 10-21, 24-26, 28-31, and 34-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected group of inventions.

### *Information Disclosure Statement*

4. The Information Disclosure Statements submitted on 7/1/05 and 7/3/06 are reviewed and a signed copy of each is attached to this office action.

### *Claim Rejections - 35 USC 112, first Paragraph*

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 2, 5 and 6 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 2 and 5-6 are drawn to a substantially purified salivary *Lu. longipalpis* polypeptide wherein the polypeptide comprises (claim 2)

- a) an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 15 (claim 6),

- b) a conservative variant of the amino acid sequence set forth as SEQ ID NO: 15.
- c) an immunogenic fragment comprising at least eight consecutive amino acids of the amino acid sequence set forth as SEQ ID NO: 15, that specifically binds to an antibody that specifically binds the amino acid sequence set forth as SEQ ID NO: 15; or
- d) the amino acid sequence set forth as SEQ ID NO: 15, and wherein administration of the polypeptide to a subject produces an immune response to *Lu. Longipalpis*, and an antigenic fragment of the polypeptide (claim 5 ).

The claimed substantially purified salivary *Lutzomyia longipalpis* ( *Lu. Longipalpis*/ *L. Longipalpis*) polypeptide comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 15, an immunogenic fragment comprising at least eight consecutive amino acids of the amino acid sequence set forth as SEQ ID NO: 15 , antigenic fragments of SEQ.ID.NO:15 read on diverse species. The specification describes an isolated salivary gland polypeptide comprising 301 amino acid sequence set forth as SEQ ID NO:15 from *Lutzomyia longipalpis*. This isolated polypeptide is described as LJL 143, the MW of unprocessed protein is 35KD while the processed protein is 32.5KD. However, the specification fails to disclose *Lu. longipalpis* polypeptide comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 15, an immunogenic fragment comprising at least eight consecutive amino acids of the amino acid sequence set forth as SEQ ID NO: 15 or antigenic fragments. The teachings of the prior art (see Soares et al , An. Acad. Bras. Ciênc. vol.75 no.3 Rio de Janeiro Sept. 2003) indicate that Leishmaniasis is a parasitic disease caused by members of the genus *Leishmania*. *Leishmania major* is transmitted to its host in vector saliva when the sand fly probes for a blood meal. The parasite evades host immunity likely through vector salivary factors and survives inside parasitophorous vacuoles in macrophages. Different gel profiles of salivary proteins and glycoproteins of sand flies including *L. longipalpis* of different species and populations of the same species, similar to those observed for Maxadilan (see page 311, right column and 312 , right column ). Some *L. longipalpis* salivary proteins reacted with Con A and WGA lectins and were found to be mannosylated, indicating a complex type of N-glycans in the glycoproteins. Hyaluronidase activity was also different in many species of sand flies, with *L. longipalpis* having the lowest activity compared to *Phlebotomus* spp. Recently, it has been demonstrated a novel function of salivary gland extracts from *L. longipalpis*, which was able to inhibit both the classical and the alternative pathways of the complement cascade. A partial characterization of the inhibitor indicates a high resistance to denaturation by heat and a molecular weight of 10-30 kDa (see page 312 , right column ). Salivary components are part of a D7 subfamily of proteins that is widespread among blood

sucking Diptera and belonging to a superfamily of pheromone/odorant binding proteins ( see page 312 , right column ).

Brodie et al (Infection and Immunity 2007, 75; 2359-2365) teach *L. longipalpis* is a complex when populations from Central and South America are compared. There are 20 different species of *Leishmania* that are transmitted by at least 30 different sand fly species, making vaccines targeting the parasites extremely complex, and thus far this approach has not been successful (see page 2359, left column).

Milleron et al teach (Am. J. Trop. Med. Hyg., 70(3), 2004, pp. 286-293) Antigenic diversity of Maxadilan , salivary protein MAX sequences. Vaccinating mice against MAX elicits a protective Th1-type response against *Leishmania*, as well as a strong anti-MAX IgG response. However, the protective abilities of one MAX variant against exposure to another variant remain to be determined. Designing a successful vaccine may mean including all of the different immunogenic forms of MAX to give blanket protection. Antigenicity appeared to be associated with amino-acid sequence variability. Thus, antigenic diversity of salivary protein from arthropod vectors, *L. longipalpis* may dictate the development of vector-based vaccines.

Based on these studies it appears that salivary proteins from different *L. longipalpis* are different and complex. Antigenic diversity exists among species of vectors *L. longipalpis*. Therefore, only an isolated and substantially purified salivary *Lu. longipalpis* polypeptide comprising the amino acid sequence set forth as SEQ ID NO: 15 but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

7. Claims 2, 5-6, 23 and the dependent claim 1 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated and substantially purified salivary *Lu. longipalpis* polypeptide comprising the amino acid sequence set forth as SEQ ID NO: 15 and a composition comprising an isolated and substantially purified salivary *Lu. longipalpis* polypeptide comprising the amino acid sequence set forth as SEQ ID NO: 15 does not reasonably provide enablement for variants of SEQ.ID.NO:15 and pharmaceutical composition comprising substantially purified salivary *Lu. longipalpis* polypeptide , SEQ.ID.NO:15. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Instant claims are evaluated for enablement using Wands analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731,8 USPQ2d 1400 (Fed.Circ.1988) as follows:

(1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack

thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

Claims 1-2 and 5-6 and 23 are drawn to a substantially purified salivary *Lu. longipalpis* polypeptide (claim 1) and a pharmaceutical composition (claim 23), wherein the polypeptide comprises an amino acid sequence at least 80% identical to the amino acid sequence set forth as SEQ ID NO: 15 (claim 6), wherein the polypeptide comprises (claim 2)

a) an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 15;

b) a conservative variant of the amino acid sequence set forth as SEQ ID NO: 15.

c) an immunogenic fragment comprising at least eight consecutive amino acids of the amino acid sequence set forth as SEQ ID NO: 15, that specifically

binds to an antibody that specifically binds the amino acid sequence set forth as SEQ ID NO: 15; or

d) the amino acid sequence set forth as SEQ ID NO: 15, and wherein administration of the polypeptide to a subject produces an immune response to *Lu. Longipalpi* and an antigenic fragment of the polypeptide (claim 5).

This means that the broadly claimed variants (i.e., fragments or 80% homology of SEQ.ID.NO:15) can be made and can be used in vector based vaccine for *Leishmania* infection. One cannot extrapolate the teaching of the specification to the full enablement of the claims because the claims as written are drawn to undefined purified salivary gland polypeptide variant or polypeptide variants SEQ ID NO : 15. (i.e., variants), and yet perform the contemplated function (Inhibition of *Leishmania*) and neither the specification nor the art of record define these variants.

The present disclosure relates to salivary proteins from sand fly vectors of *Lutzomyia longipalpis* (*Lu. longipalpis*) and the nucleic acids that encode these proteins. The current specification describes the claimed protein, L JL 143, SEQ.ID.NO:15 from *L. longipalpis* is a 35KD unprocessed protein while the processed protein is 32.5KD.

As drawn to sequences having 80 % identity, conservative variants or fragments of SEQ.ID.NO:15, it means that claimed sequences are broadly drawn undefined isolated salivary protein SEQ ID NO: 15 that is specific for *Lu. longipalpis*. However, the specification fails to teach variants of SEQ ID NO: 15 or pharmaceutical composition comprising salivary polypeptide, SEQ.ID.NO:15.

As drawn to variants of SEQ.ID.NO:15, the claims are broadly drawn to undefined isolated purified salivary polypeptide having at least 80% identity to SEQ ID NO:15, conservative variants thereof and fragments, however the specification fails to disclose what are critical amino

acids in a polypeptide comprising 301 amino acid sequence set forth as SEQ ID NO:15 from *Lutzomyia longipalpis* that can be used.

As drawn to pharmaceutical composition comprising the salivary polypeptide SEQ.ID.NO:15 and variants of said polypeptide, the specification fails to provide an enabling disclosure for pharmaceutical composition because it fails to provide any guidance regarding how to use the claimed composition for preventing, alleviating or treating Leishmaniasis. The teachings of the prior art (see Soares et al, An. Acad. Bras. Ciênc. vol.75 no.3 Rio de Janeiro Sept. 2003) indicate that Leishmaniasis is a parasitic disease caused by members of the genus *Leishmania*. *Leishmania major* is transmitted to its host in vector saliva when the sand fly probes for a blood meal. The parasite evades host immunity likely through vector salivary factors and survives inside parasitophorous vacuoles in macrophages. Different gel profiles of salivary proteins and glycoproteins of sand flies including *L. longipalpis* of different species and populations of the same species, similar to those observed for Maxadilan (see page 311, right column and 312, right column). Some *L. longipalpis* salivary proteins reacted with Con A and WGA lectins and were found to be mannosylated, indicating a complex type of N-glycans in the glycoproteins. Hyaluronidase activity was also different in many species of sand flies, with *L. longipalpis* having the lowest activity compared to *Phlebotomus* spp. Recently, it has been demonstrated a novel function of salivary gland extracts from *L. longipalpis*, which was able to inhibit both the classical and the alternative pathways of the complement cascade. A partial characterization of the inhibitor indicates a high resistance to denaturation by heat and a molecular weight of 10-30 kDa (see page 312, right column). Salivary components are part of a D7 subfamily of proteins that is widespread among blood sucking Diptera and belonging to a superfamily of pheromone/odorant binding proteins (see page 312, right column). Brodie et al (Infection and Immunity 2007, 75; 2359-2365) teach *L. longipalpis* is a complex when populations from Central and South America are compared. There are 20 different species of *Leishmania* that are transmitted by at least 30 different sand fly species, making vaccines targeting the parasites extremely complex, and thus far this approach has not been successful (see page 2359, left column). Milleron et al teach (Am. J. Trop. Med. Hyg., 70(3), 2004, pp. 286-293) Antigenic diversity of Maxadilan, salivary protein MAX sequences. Vaccinating mice against MAX elicits a protective Th1-type response against *Leishmania*, as well as a strong anti-MAX IgG response. However, the protective abilities of one MAX variant against exposure to another variant remain to be determined. Designing a successful vaccine may mean including all of the different immunogenic forms of MAX to give blanket protection. Antigenicity appeared to be associated with amino-acid sequence variability. Thus, antigenic diversity of salivary protein from arthropod vectors, *L. longipalpis* may dictate the development of vector-based vaccines.

Based on these studies, it appears that salivary proteins from different *L. longipalpis* are different and complex. Antigenic diversity exists among species of vectors *L. longipalpis*. The current specification only indicate that the claimed protein L JL 143 from *L. longipalpis* is a 35KD unprocessed protein while the processed protein is 32.5KD . Therefore, the claimed variants and the pharmaceutical composition would prevent/treat/cure the infection caused by *Leishmania* is not predictable. The specification provides no disclosure how to vaccinate human against *Leishmania* (i.e., various species) using the claimed composition because it fails to provide guidance whether the claimed composition provides protection against species of *L. longipalpis* that transmit *Leishmania*. The state of the art is devoid of teaching variants of salivary *L. longipalpis* polypeptide, SEQ.ID.NO: 15 that are used in *Leishmania* infection . The protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (Bowie et al. Science, Vol. 247: 1990; p. 1306; p. 1308) and is well outside the realm of routine experimentation and the result of such modifications is unpredictable based on the instant disclosure. Absent such demonstration, the invention would require undue experimentation to practice as claimed. In view of the above, one of skill in the art would be forced into undue experimentation in order to practice the invention as claimed.

**Claim Rejection - 35 USC 102**

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Charlab et al 1999 Proc Natl Acad Sci U S A. 1999 Dec 21; 96(26): 15155-60.

Claim 1 is drawn to a substantially purified salivary *Lu. longipalpis*

Charlab et al disclose substantially purified salivary apyrase *L.longipalpis* polypeptide (see abstract and page 15157, left column) and thus read on claim 1.

9. Claims 23 and 1 are rejected under 35 U.S.C. 102(b) as being anticipated by Sousa et al Mem. Inst. Oswaldo Cruz vol.96 no.7 Rio de Janeiro Oct. 2001.

Claim 1 is discussed supra. Claim 23 1 is drawn to a pharmaceutical composition comprising a substantially purified salivary *Lu. longipalpis* polypeptide.

Sousa et al disclose a pharmaceutical composition comprising substantially purified recombinant Maxadilan from *Lu. longipalpis* in a pharmaceutical carrier , PBS (see page 997, right column, figure 1). Thus , the prior art anticipated the claimed invention.



**Remarks**

10. Claims 1-2, 5-6 and 23 are rejected.

Claim 4 is objected as it depends from a rejected base claim. The prior art does not teach or suggest an isolated and purified salivary *Lu. Longipalpis* polypeptide comprising the amino acid sequence SEQ.ID.NO:15.

**Conclusion**

11. Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform to the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The Right Fax number is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PMR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PMR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Padma Baskar Ph.D., whose telephone number is ((571) 272-0853. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 6.30 a.m. to 4.00 p.m. except First Friday of each bi-week.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on (571) 272-0898. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600



Padma Baskar Ph.D.



SHANON FOLEY  
SUPERVISORY PATENT EXAMINER  
TECHNOLOGY CENTER 1600